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EXAMINER
WEHBE, ANNE MARIE SABRINA

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/724,965	Applicant(s) Lonberg
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 13, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *57-75* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *57-75* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response to the restriction requirement received on 1/13/03 has been entered. Claims 17-56 have been canceled. New claims 57-75 have been added. Claims 57-75 are pending in the instant application. Applicant's election without traverse of the subject matter of Group I is acknowledged. Applicant's new claims are all directed to the elected subject matter. Therefore, claims 57-75 are currently under examination. An action on the merits follows.

Specification

The applicant is notified that pages 136-140 appear to be missing from the specification as filed. The applicant is requested to provide pages 136-140 in response to this office action.

Priority

This application claims benefit to numerous parent applications. Please note, however, that the subject matter of claims 59-60, 66-67, and 74-75 are only entitled to claim the benefit of priority to parent application 07,990,860, filed on 12/16/92. The applicant is reminded that in order to receive the benefit of an earlier filing date under 35 U.S.C. 120, the second (child) application must be an application for a patent for an invention which is also disclosed in the first

application (the parent or provisional application), and the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). The subject matter of claims 59-60, 66-67, and 74-75, which is directed to a transgene comprising a human 3' kappa enhancer segment and specifically a 4kb BamHI human 3' kappa enhancer segment, is not disclosed in the parent applications filed before the 07/990,860 application. The applications filed before 12/92 disclose unrearranged germline segments of the human kappa light chain locus which only extend 9kb past the 3' end of the kappa constant region gene. Further, the applications filed before 12/92 state that the location and sequence of the human kappa constant region gene was unknown. Judde et al. published the location and sequence of the human kappa 3' enhancer in November of 1992. Judde et al. states that the enhancer is located 12 kb downstream of the kappa constant region gene. The 07/990,860 application, filed in December of 1992, references the Judde publication. Thus, claims 59-60, 66-67, and 74-75 are only entitled to claim the benefit of priority to parent application 07,990,860, filed on 12/16/92.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 57-58, 62-65, and 69-73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-3 of U.S. Patent No. 5,625,126 (4/29/97), hereafter referred to as the '126 patent. Although the conflicting claims are not identical, they are not patentable distinct from each other for the following reasons. The applicant claims a transgenic animal comprising a transgene which comprises a plurality of human light chain V genes, a plurality of light chain J genes, and a human light chain C gene. The applicant further claims said transgenic animals wherein the animal is a mouse, wherein the light chain genes are kappa light chain genes, and wherein the non-human transgenic animal further produces a repertoire of human heavy chain polypeptides.

Claims 2-3 of the '126 patent are both broader and narrower than the instant claims. Claims 2-3 recite a transgenic mouse whose genome comprises a transgene comprising a plurality of human heavy chain V genes, a plurality of human heavy chain D genes, a plurality of human heavy chain J genes and a human heavy chain constant region mu gene, and which further comprises an integrated human kappa light chain transgene. The claims differ from the instant invention by not specifically reciting that the human light chain transgene comprises a plurality of human light chain V genes, a

plurality of light chain J genes, and a human light chain C gene. However, the specification of the '126 patent clearly teaches human kappa light chain transgenes which comprise a plurality of human light chain V genes, a plurality of light chain J genes, and a human light chain C gene ('126 specification, columns 57-60). Thus, the transgenic mice recited in claims 2-3 of the '126 patent clearly encompass and render obvious the transgenic non-human animals of instant claims 57-58, 62-65, and 69-73.

Claims 57-58, 62-65, and 69-73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of U.S. Patent No. 5,789,650 (8/4/98), hereafter referred to as the '650 patent. Although the conflicting claims are not identical, they are not patentable distinct from each other for the following reasons. The applicant claims a transgenic animal comprising a transgene which comprises a plurality of human light chain V genes, a plurality of light chain J genes, and a human light chain C gene. The applicant further claims said transgenic animals wherein the animal is a mouse, wherein the light chain genes are kappa light chain genes, and wherein the non-human transgenic animal further produces a repertoire of human heavy chain polypeptides.

Claim 5 of the '650 patent is both broader and narrower than the instant claims. Claim 5 recites a transgenic mouse whose genome comprises a unrearranged human immunoglobulin locus comprising a plurality of human heavy chain V genes, a plurality of human heavy chain D genes, a plurality of human heavy chain J genes and a human heavy chain constant region mu gene, and which

further comprises a human kappa light chain locus. The claims differ from the instant invention by not specifically reciting that the human light chain locus comprises a plurality of human light chain V genes, a plurality of light chain J genes, and a human light chain C gene. However, the specification of the '650 patent clearly teaches human kappa light chain YACs which comprise a plurality of human light chain V genes, a plurality of light chain J genes, and a human light chain C gene ('650 specification, columns 41-42). Thus, the transgenic mice recited in claim 5 of the '650 patent clearly encompasses and render obvious the transgenic non-human animals of instant claims 57-58, 62-65, and 69-73.

Claims 57-58, 61-65, and 68-73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,877,397 (3/2/99), hereafter referred to as the '397 patent. Although the conflicting claims are not identical, they are not patentable distinct from each other for the following reasons. The applicant claims a transgenic animal comprising a transgene which comprises a plurality of human light chain V genes, a plurality of light chain J genes, and a human light chain C gene. The applicant further claims said transgenic animals wherein the animal is a mouse, wherein the light chain genes are kappa light chain genes, and wherein the non-human transgenic animal further produces a repertoire of human heavy chain polypeptides. In addition, the applicant claims said transgenic animals wherein the endogenous heavy chain and light chain loci are inactivated.

Claims 1-7 of the '397 patent recite a transgenic mouse whose genome comprises a transgene comprising a plurality of human heavy chain V genes, a plurality of human heavy chain D genes, a plurality of human heavy chain J genes and a human heavy chain constant region mu gene, and which further comprises an integrated human kappa light chain transgene. Claims 1-7 differ from the instant invention by not specifically reciting that the human light chain locus comprises a plurality of human light chain V genes, a plurality of light chain J genes, and a human light chain C gene. However, the specification of the '397 patent clearly teaches human kappa light chain transgenes which comprise a plurality of human light chain V genes, a plurality of light chain J genes, and a human light chain C gene ('650 specification, columns 41-42). Thus, the transgenic mice recited in claims 1-7 of the '397 patent clearly encompasses and render obvious the transgenic non-human animals of instant claims 57-58, 62-65, and 69-73.

Claims 8-10 recite a transgenic mouse which comprises a transgene comprising a plurality of human heavy chain V genes, a plurality of human heavy chain D genes, a plurality of human heavy chain J genes and a human heavy chain constant region mu gene, and which further comprises a human kappa chain transgene with human V gene segments, human J gene segments, and a human C coding exon, wherein both the endogenous heavy and light chain loci are inactivated. Thus, claims 8-10 which are limited to transgenic mice represent a species of the instant claims and as such render instant claims 57-58, 61-65, and 68-73 obvious.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-62, 64-69, and 71-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification broadly teaches transgenic non-human animals which comprise germline segments of the human Ig heavy or light chain loci, and in particular on unrearranged segments of the human kappa light chain locus, in their genome. The specification further discloses transgenic non-human animals in which the endogenous light and/or heavy chain loci are inactivated. Specifically, the specification discloses the use of germline segments of the human Ig heavy chain and light chain locus which comprise a plurality of heavy chain or light chain V genes respectively. Please note, the transgenes described in the specification read on transgenes which include the entire human light chain kappa or lambda loci.

The specification does not provide an enabling disclosure for making or using transgenes comprising the entire human Ig light chain loci. The specification discloses the

use of unrearranged germline sequences comprising the human immunoglobulin light chain kappa or lambda loci. The specification fails to provide any guidance for genomic sequences encoding V, J, or C region genes of the immunoglobulin lambda locus. Furthermore, the specification only provides guidance for a single unrearranged DNA sequence derived from the human kappa light chain locus which comprises more than one human kappa light chain V gene, pKC2. The pKC2 transgene comprises 2 V kappa light chain genes. The specification fails to provide sufficient guidance for transgenes, YACs, or other types of genetic constructs which encode distal human variable region genes for the kappa locus or which encodes the human variable region genes in their entirety for either the kappa or lambda locus. At the time of filing, physical mapping, cloning, and sequencing of the entire human light chain kappa and lambda loci had not been accomplished. The applicant is reminded that case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves. *In re Gardner* 166 USPQ 138 (CCPA) 1970. Therefore, in view of the lack of teachings in both the art and the specification for the complete sequence of the functional V kappa or lambda segment genes on chromosomes 2 and 22 respectively, the lack of guidance for operably linking nucleotide sequences encoding V kappa light chain genes distal to the J kappa light chain region, and the breadth of the claims, it would have required undue experimentation to obtain and use a transgene encoding any fragment of the unrearranged germline kappa or lambda loci

comprising the J regions and C gene operably linked to any or all V segment genes to make a transgenic non-human animal according to the instant invention.

The specification does not provide an enabling disclosure for producing any and all transgenic non-human animals other than transgenic mice. As noted above, the specification teaches transgenic non-human animals which comprise a transgene comprising unrearranged segments of human light chain locus, and which further comprise a inactivated endogenous light chain locus. The specification discloses that embryonic stem cells or other types of embryonal cells can be transfected *in vitro* with a DNA vector capable of homologously recombining into the genome, injected into a blastocyst, and implanted into a pseudopregnant female animal resulting in progeny with transgenic DNA inserted into one or more copies of the targeted gene of interest. The specification does not provide guidance for identifying and isolating embryonic stem cells from species other than the mouse, or for identifying other embryonal cells which are capable of contributing to the germline of any animal. At the time of filing, Campbell et al. teaches that, "[i]n species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species....However, as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse" (Campbell et al. (1997)Theriology, Vol. 47 (1), page 65, paragraph 2). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce

transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs, cows, or platypus, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic mammals using ES cell technology.

It is further noted that the specification discloses that microinjection of embryos can be used to produce transgenic animals according to the instant invention. However, at the time of filing, the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al. (1994) Reprod. Fertil. Dev., Vol. 6, 585-588). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems as homologous recombination events are even rarer than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos or zygotes, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention other than transgenic mice.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64-71 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The claims recite a transgenic non-human animal which comprises a human light chain immunoglobulin transgene, wherein said non-human animal further produces a repertoire of human heavy chain polypeptides that pair with said light chain polypeptides to form a repertoire of human immunoglobulins in said non-human animal. The claims as written omit the presence of a human immunoglobulin heavy chain transgene in the genome of the transgenic non-human animal. In the absence of an unrearranged human heavy chain locus transgene in the genome of the transgenic animal, the non-human animal would be incapable of producing human heavy chain polypeptides.

No claims are allowed.

The claims as written appear to be free of the prior art of record, as the art of record does not appear to teach a transgene or transgenic non-human animals which comprises a plurality of human V light chain genes, a plurality of human J light chain genes, and a human V constant region gene.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached

Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER